AWARD NUMBER: **W81XWH-15-1-0601**

TITLE: **Blink prosthesis for facial paralysis patients**

PRINCIPAL INVESTIGATOR: **Daniel McDonnall, Ph.D.**

CONTRACTING ORGANIZATION: **Ripple LLC**
Salt Lake City, UT 84106-2318

REPORT DATE: **October 2016**

TYPE OF REPORT: **Annual report**

PREPARED FOR: **U.S. Army Medical Research and Materiel Command**
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual	9/30/2015 – 9/29/2016

4. TITLE AND SUBTITLE
Blink prosthesis for facial paralysis patients

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0601

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Daniel McDonnall, Ph.D.

E-Mail: danny@rppl.com

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Ripple LLC
Salt Lake City, UT 84106-2318

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Ripple is developing an implantable stimulator to restore functional eye blink in patients with unilateral facial nerve paralysis. The system will electrically stimulate the paretic eyelid when EMG electrodes detect normal blink from the contralateral eye, producing synchronous blink. The proposed blink prosthesis is intended for patients with facial nerve damage who suffer long-term disfigurement and dysfunction due to the loss of the ability to convey facial expression and produce eye blink.
In the first year of the project, we have developed a hermetic implantable ceramic package to house the stimulation/recording electronics. The package has been impact tested to confirm the ceramic material will be strong enough for permanent implantation. We have also verified the wireless data and power transmission system is robust and efficient. The system can transmit high-bandwidth signals, tolerate misalignment, and meet requirements for implant thermal discharge.

15. SUBJECT TERMS
facial paralysis, neuroprosthetics, functional electrical stimulation, medical device, Bell's Palsy

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	13	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

1. INTRODUCTION

Patients suffering from facial nerve damage experience substantial disfigurement and dysfunction due to the inability to produce eye blink and convey facial expression. The loss of the blink response is very painful and predisposes patients to corneal exposure and dry eye complications that are difficult to effectively treat. The proposed innovation will provide a fundamental improvement in the treatment of ophthalmic manifestations of patients with facial paralysis. These improvements will apply to both the aesthetic and functional use of the paralyzed eyelid by preventing painful dry eye complications and profound facial disfiguration. The goal of this program is to create an implantable blink prosthesis to restore functional eye blink in patients with paralysis on one side of their faces. The system will use electrodes implanted in the eyelid to stimulate the adjacent muscles to close the eye. Another set of electrodes implanted in the healthy eyelid will listen for the onset of a blink and send a timing signal to the electronic system to turn on the stimulator to produce a bilateral symmetric blink in the paralyzed eye.

2. KEYWORDS

facial paralysis, neuroprosthetics, functional electrical stimulation, medical device

3. ACCOMPLISHMENTS

Major Goals

Major Task 1: Verification of system power efficiency and thermal dissipation
Design of transceiver for coil-to-coil distances of 15mm, up to 1 cm of misalignment, and coil angles up to 30 degrees

Milestone(s) Goals:

	Goal	Results
Transmitted power efficiency	35%	25%-35%
Total power usage	$\geq$ 50 mW	25 mW
Surface power dissipation density	5 mW/cm^2	2.5 mW/cm^2

We made the design decision to reduce the size of the implanted package to make the device more acceptable to consulting facial plastics and ophthalmic surgeons. As a result we had to decrease the size of the implanted coil. The small coil decreased the efficiency of power transmission. However, we were able to substantially minimize the power usage of the device, thus the total power consumption of a 25 mW implant at 25% efficiency is still 44% more efficient than a 50 mW implant with 35% efficiency.

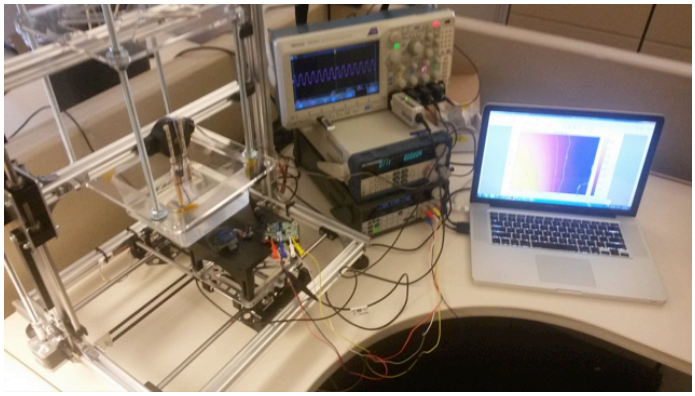
Major Task 2: Implant package hermeticity
Milestone(s) Achieved:

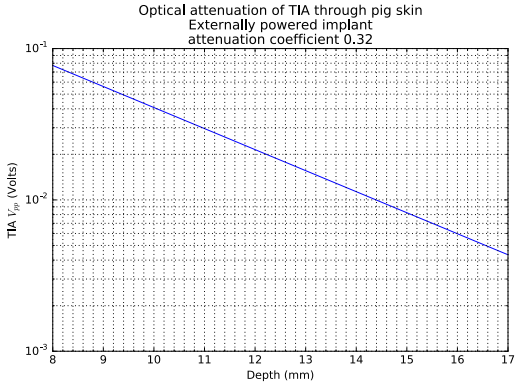
The ceramic package with the sealed feedthrough pin header met MIL 883 for implantable electronic medical device hermetic integrity. The ceramic package has been impacted tested with a 2 J force; the package remains mechanically intact and maintains hermetic integrity.

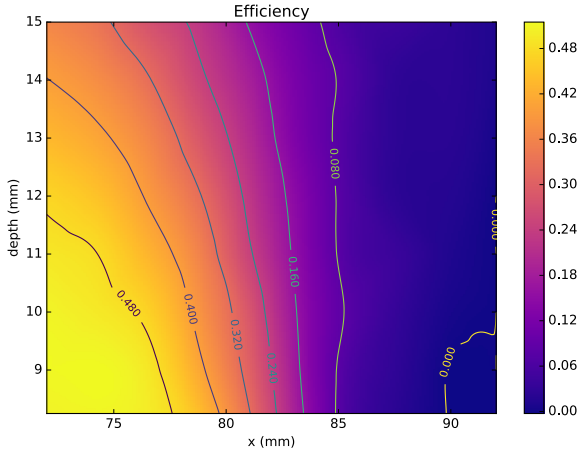
Goals Accomplished

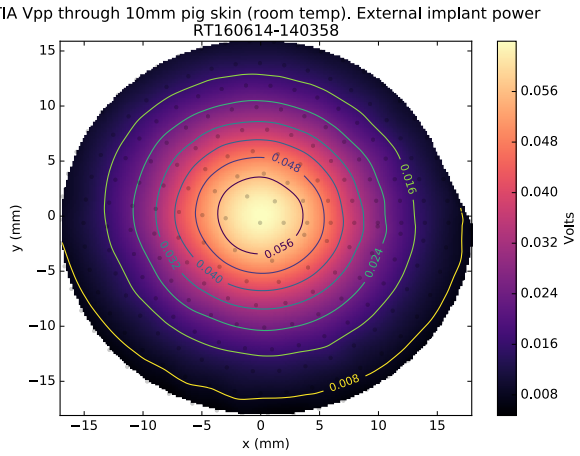
Transmitted power efficiency

To characterize power efficiency as a function of distance between coils, we have developed an automated robotic testing system to evaluate candidate external transceiver circuit designs. Shown below is an implant in a saline bath and a coil driver circuit connected to a candidate transceiver coil. The coils are on an XYZ stage to adjust relative position. An oscilloscope sits on top of an electronic load instrument used to provide a controlled load to the implant. Underneath the instrument is a power supply used to drive the transceiver coil with a known voltage and current. This setup allows for testing of external transceiver circuit designs. Additionally, we can generate 1) spatial maps showing power transfer efficiencies on points from an x-z slice, and 2) efficiency maps over the transceiver vs. implant voltage parameter space taken across spatial points. The setup also tests the IR link in an automated way, producing a packet decode region map.









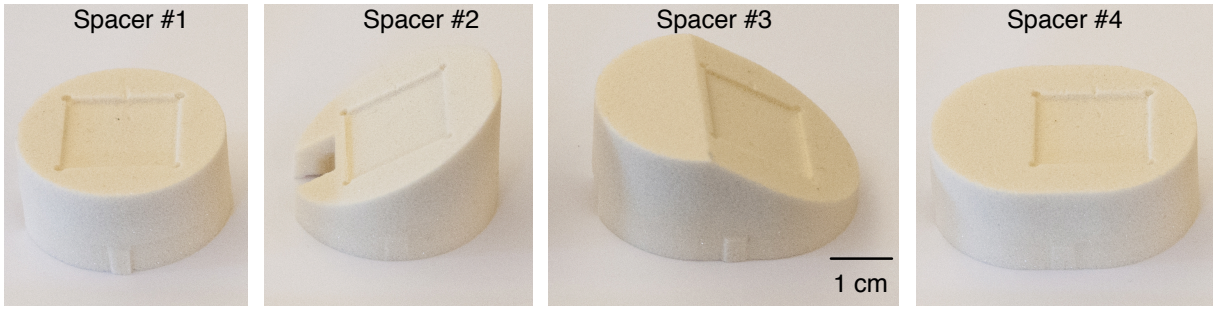
The efficiency graph shows the power transfer efficiency at a fixed power from a class D transceiver into the implant coil. It is spatially resolved on the half-plane that intersects the axis perpendicular to the coils (which are parallel). The depth is the displacement between the coil centers. Prior to running the experiment the robot identifies the location of maximum power transfer and uses that as the origin of the coordinate system. The constant power is not regulated by the circuit itself; the automated experiment control algorithm adjusts the driver voltage with an optimization algorithm to get the desired power set point with the implant regulated to 3.6V. Once the power is adjusted, an efficiency measurement is taken.

The TIA Vpp graph measures the peak-to-peak voltage of the communication signal coming from the photodiode before the main amplifier stage with pig skin blocking the optical field. A similar zero-finder is used in this experiment to hunt for the origin. This signal is spatially resolved by moving the transceiver in a spiral pattern from the origin to the maximum search radius.

The optical attenuation graph assumes the optical attenuation of pig skin follows the Beer-Lambert law to get an estimate of what the TIA output will be at different thicknesses of pig skin. It is a sparse graph, interpolating two data points, 15mm and 10mm pig skin depths. The graph is generated at the best-case position of maximum optical transmission.

Worst-case coil displacement

To ensure the system could meet the efficiency and thermal dissipation requirements, we tested the system in a series of worst-case use scenarios of coil-to-coil distance, coil alignment, and relative coil angle. A series of spacers were constructed for the coils to determine if the system could function with external-to-implant coil-to-coil distances of up to 15 mm, up to ±1 cm of misalignment, and coil angles up to ±30 degrees.



Spacer #1: The external and implant coils are positioned parallel to each other, horizontally aligned center-to-center, and separated by a 15 mm vertical gap.

Spacer #2: The implant coil is tilted at 30 degrees relative to the external coil. The coils are horizontally aligned center-to-center and separated by a 15 mm vertical gap, measured from the center of the external coil to the center of the implant coil.

Spacer #3: The implant coil is tilted at 30 degrees relative to the external coil. The coil centers are horizontally offset by 10 mm (misaligned). The coils are separated by a 15mm gap between two planes, measured vertically from the center of the external coil to the center of the implant coil.

Spacer #4: The external and implant coils are positioned parallel to each other. The coil centers are horizontally offset by 10mm (misaligned). The coils are separated by a 15mm gap, measured vertically from the center of the external coil to the center of the implant coil.

Having demonstrated the power transmission system operated within nominal goals with the spacers. We repeated the alignment testing using cadaveric swine skin of different thicknesses to model wireless transmission of power and data signals at different implantation depths. In this configuration our system has demonstrated infrared communication with zero dropped packets at (a) 2 kS/s, 12 bits/sample on 32 channels, with 1.5 cm implant depth and 10 mm displacement, or (b) 30 kS/s, 12 bits/sample on 32 channels, with 1.0 cm implant depth and 7 mm displacement, or (c) 30 kS/s, 12 bits/sample on 32 channels, with 1.5 cm implant depth and 0 mm displacement. Using a 2 kS/s sample rate, which is the most common use case, we now meet our design requirements. While the implant PCB is sent out for fabrication, we are continuing with our efforts to improve the efficiency of the external transceiver which provides combined inductive powering and infrared data reception. The external transceiver is using a new class D coil driver circuit. We are currently investigating the effects of the ferrite disc, specifically the efficiency vs. shielding tradeoff.

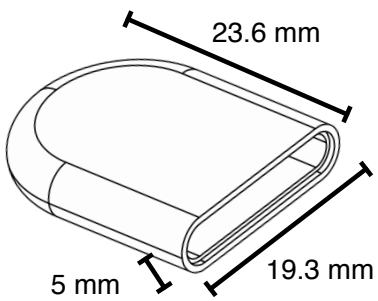
Surface power dissipation density

Most medical standards for implanted electronic devices require the implant must not rise more than 1 ^{0}C above surrounding tissue, and this corresponds to device surface dissipation flux levels of 50 to 200 mW per cm^2 depending on the implanted body area. We have specified meeting a requirement of having a system surface dissipation density no greater than 5 mW/cm^2. The thermally conductive circuit components in the interior of the device will make the overall thermal profile uniform around the electronics package. For an implantable enclosure with a radius of 9mm and overall thickness of 4mm, the surface area for the implanted electronics package is 10.01 cm^2.

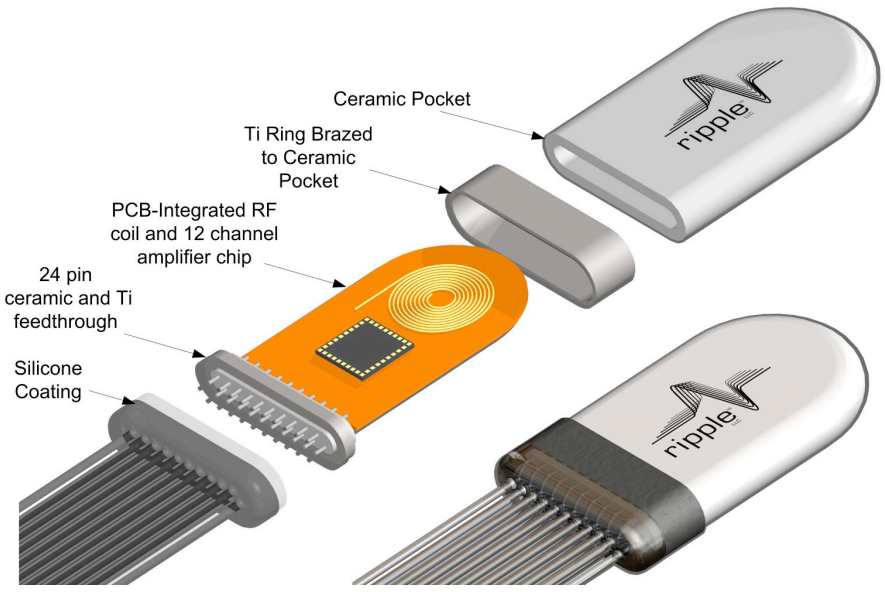
The system operated 2.5 mW/cm^2 in all test configurations. Coil misalignment scenarios had the largest impact on power efficiency, although the system was relatively immune to coil distance changes and relative coil angles.

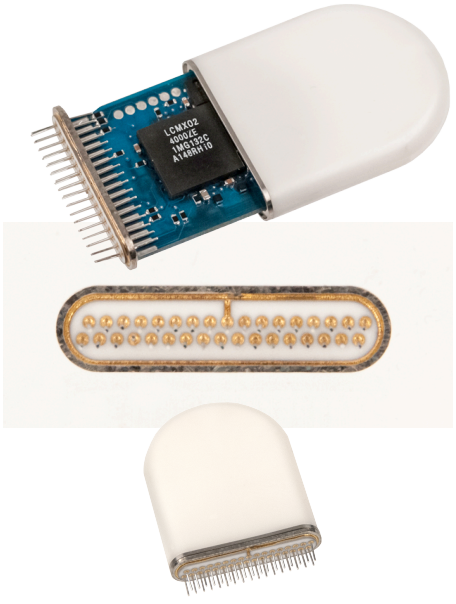
Hermetic Integrity of Ceramic Enclosure

The ceramic enclosure of the implanted transmitter is fabricated by Pacific Aerospace, the company that produced the implantable package of the original Med El cochlear implant. The enclosure is composed of Yttria-stabilized zirconia (Y-TZP), a material also commonly used in hip and other joint prostheses, and has a pocket-like shape and assembly process that is very similar to the Med El device. In contrast to titanium enclosures, a ceramic enclosure is transparent to RF energy, and its use in this program will allow for more efficient inductive powering in a small, low-cost, integrated package. The implant enclosure is about 19 x 24 x 5 mm, and similar in volume to a stack of two U.S. quarters (see dimensioned drawing and picture of implant ceramic enclosure). These pocket- formed ceramic packages are also quite strong, as demonstrated by similar cochlear devices that meet head impact safety requirements.



For assembly, a titanium ring is brazed to the lip of the ceramic pocket rim using a gold alloy. This bond creates a biocompatible hermetic seal to the ceramic pocket, and the ring creates an interface for the final seal of the feed-through assembly. The feed-through assembly consists of an alumina ceramic plate with 34 brazed wires protruding through it and a titanium ring brazed around the edges. Electronic boards are attached to the feed-through wires on the inside ends, and the electronics slide into the ceramic pocket until the two titanium rings are flush with each other. The titanium rings are laser welded in a 75% argon, 25% helium atmosphere to create a hermetic seal.



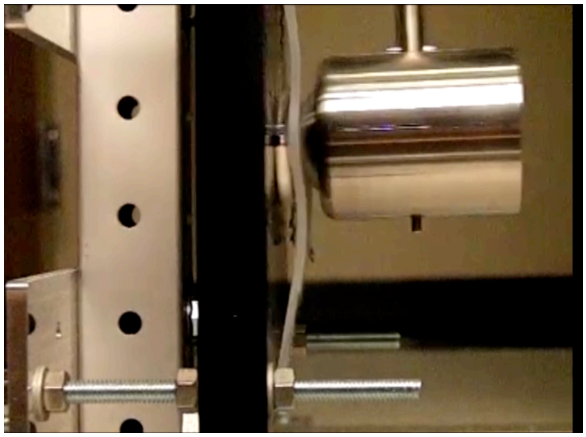


The electrode leads are laser welded to the feed-through pins, and the bonding area is potted in an epoxy header to protect and insulate the wire bonds. The laser welding allows precise attachment of the electrodes in the same assembly facility without introducing contaminants, such as solder or flux, into the bonding area. Ripple LLC has contracted with Litron, Inc. (Agawam, MA) to assemble the electronics, electrodes, hermetic package, and epoxy header. Litron is an ISO 13485:2003 certified company that specializes in assembly and testing of hermetic implantable medical devices.

Impact testing of ceramic enclosure

Hermeticity of the electronics package is vital to an extended life device. To verify hermeticity, a third-party helium leak test was performed per MIL Standard 883K. Thirteen devices were used for the testing, and all devices passed the hermeticity requirements of 5 x 10-9 atm cc/sec. Future assembled devices will all be verified for hermeticity by third-party helium leak testing.

To confirm our package design can maintain its hermeticity over time it needs to survive the forces and impacts it may experience in its lifetime. Cochlear devices have a long history as long-term implants located below the skin. Cochlear implants have the added complexity of being located directly onto the hard skull making impacts difficult to absorb. As a result we determined the impact test protocol used for cochlear implants to be a valid method for verifying our design.



In accordance with ISO 14708-7:2013 particular requirements for a cochlear implant systems, four devices were impacted two at the center of the device and two at the “weakest point” determined to be directly on the feedthrough header. Each test was conducted with a 2.5J impact a new requirement as of 2015 up from the previous requirement of 1.5J.

In addition to a 40X visual inspection a third party tested the impacted devices to the same MIL-883K standard and showed no effect from the impacts.

Training and Professional Development

Nothing to report

Dissemination of Results

Nothing to report

Year 2 Goals

Major Task 3: Safety and electromagnetic compatibility standards compliance

In year two, the final electronics for the external controller will be completed, along with the software necessary for basic diagnostic and control functions of the implant. The controller will also include a micro-USB interface port for charging the internal battery and configuring the system via a PC. The internal electronics for the device will be based on commercial discrete components and a low-power microcontroller.

The external housing for the controller will be an injection molded shell, made to contain the batteries and electronics, and a softer rubber tip to fit over the ear. The external controller will be very similar in design to signal processors such as the Cochlear™ Nucleus®. The external inductance coil will consist of two injection-molded pieces: an over-molded coil and an alignment magnet holder. The user will be able to adjust the pressure exerted by the coil by adjusting the distance of the magnet from the skin surface. The coil will attach to the external package by a short cable with a connector. The coil can be placed under the hair and can be easily removed to disengage the device at night while the user sleeps.

Electrical Development and Third-Part Verification Testing

In year one, the final electronics for the implant and the external controller will be completed. At the end of year two, the final system will be officially third-party tested for compliance with the IEC 60601 family of electronic medical device standards, including:

- IEC 60601-1 Medical electrical equipment - Part 1: General requirements for safety
- IEC 60601-1-2 Medical electrical equipment - General requirements for safety - Collateral standard: Electromagnetic compatibility (For radiated emissions, the systems will be tested compliance for FCC Part 15 and CISPR Class A requirements.)
- IEC 60601-1-4 Medical electrical equipment - General requirements for safety - Collateral Standard: Programmable electrical medical systems.
- BS EN 45502-1 Active implantable medical devices -- Part 1: General requirements for safety, marking and for information to be provided by the manufacturer

Major Task 4: Biocompatibility and Sterilization validation

Biocompatibility testing

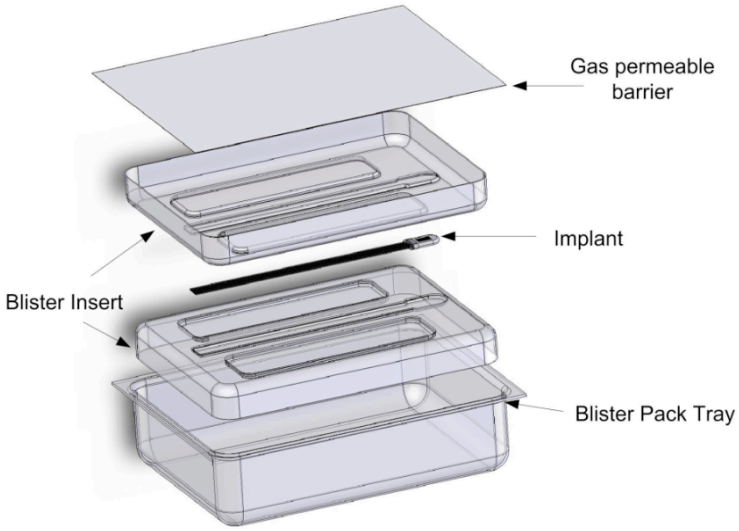
Once material-complete prototypes are finished, third-party biocompatibility testing will begin. When the final packaging is available, sterilization validation will begin. The tests performed will be dictated by the recommendations of ISO 10993 based on implant device category Tissue/Bone contact; >30 days contact duration. The following are the tests that will be performed by Nelson Laboratories under GLP (Good Laboratory Practice):

- Cytotoxicity: MEM Elution (ISO/USP)
- Sensitization: Maximization (ISO) (w/2 extracts)
- Sensitization: Local Lymph Node Assay (w/2 extracts)
- Irritation: Intracutaneous Reactivity (ISO) (w/2 extracts)
- Systemic Toxicity: Systemic Injection (ISO/USP) (w/2 extracts)
- Systemic Toxicity: Material Mediated Pyrogen (ISO)
- Subacute Toxicity
- Genotoxicity: Ames test (w/ 2 extracts)
- Genotoxicity: Chromosomal Aberration (w/2 extracts)
- Genotoxicity: Mouse Lymphoma (w/2 extracts)
- Implantation w Histopathology: (ISO) 12 Week Observation

Sterilization validation

Finished devices will be packaged for sterilization and shipping in a standard thermoformed plastic tray with a blister insert and peel-away gas permeable sheet (e.g., Tyvek or similar). Custom packaging in this style is widely available in the medical industry and packages for this program will be provided by Ventrex. The package will also include cavities for wire cutters and other components that may be added for surgical procedures. Once populated and sealed, the packages will be gas (EtO) sterilized, and packaged in corrugated boxes for protection during shipping. Sterilization testing will be completed at Nelson Laboratories to confirm residual EtO levels and microbial endotoxin testing comply with ANSI/AAMI ST 72:2011. In previous pre-IDE meetings with the FDA we have established the details for numbers of devices needed for this testing.

Mechanical testing of the implant for vibration resistance will be performed by Rocky Mountain Test Solutions in Roy, Utah, in accordance with CENELEC HD 323.2. Durability and shipping tests of the packaging for the implant and external device will also be performed by Rocky Mountain Test Solutions in accordance with the ISO 11607 standard, including Shock/Drop, Vibration, and Compression Testing.



4. IMPACT

Impact on development of principle disciplines

The goal of this program is to create an implantable stimulator device to restore functional eye blink in patients with unilateral facial nerve paralysis. The system will electrically stimulate the paretic eyelid when EMG electrodes detect normal blink from the contralateral eye to produce a synchronous blink. The implant will consist of a thin, ceramic package placed subcutaneously above the hairline with an EMG electrode pair for detecting contralateral blink and a thin-film stimulating array implanted on the paretic orbicularis oculi muscle (OOM).

We have designed this system to include a novel conductive polymer stimulation array, which is implanted along the length of the palpebral component of the paretic OOM. Multiple stimulation sites will allow clinicians the ability to selectively activate all necessary muscle tissue to evoke spontaneous blink via a diffuse injection of low levels of current across the array. The system will include a pair of EMG recording electrodes implanted into the contralateral intact OOM to detect normal reflexive blink. This detected blink single will be relayed to implanted circuitry inserted above the hairline in the scalp, which will trigger stimulation causing a synchronous blink. The device will be powered by a small, external module worn behind the ear, which activates the implanted with a wireless reflected impedance signal and provides a user interface to control stimulation intensity.

The market for these devices is relatively small with annual patient populations on the order of a few thousand per year. For these patients, however, the availability of this technology will provide a profound improvement in quality of life and reduction of total care costs due to complications related to exposure of the affected eye.

Impact on other disciplines

Nothing to report

Impact on technology transfer

Nothing to report

Impact on broader society

Nothing to report

5. CHANGES/PROBLEMS

Changes in approach

We made the design decision to reduce the size of the implanted package to make the device more acceptable to the facial plastics and ophthalmic surgeons we consulted. As a result we had to decrease the size of the implanted coil. The small coil decreased the efficiency of power transmission. However, we were able to substantially minimize the total power usage of the device, thus the total power consumption of a 25 mW implant at 25% efficiency is still 44% more efficient than a 50 mW implant with 35% efficiency.

Actual or anticipated problems

Nothing to report

Significant changes of expenditures

Nothing to report

Changes in use of vertebrate animals

Nothing to report

6. PRODUCTS

Publications and presentations

Work was presented in a poster at the Neural Interface Conference in Baltimore, MD in July 2016.

Website

http://rippleneuro.com/blink-prosthesis

Technologies or techniques

The wireless and hermetic package components will be part of the eventual medical device.

Inventions, patents, and/or licenses

Nothing to report

Other products

Nothing to report

6. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

Individual contributions

Name:	Alexander Thiessen		Name:	Brian Crofts
Project Role:	Manufacturing Engineer		Project Role:	Electrical Engineer
Months:	1		Months:	8
Contribution:	Dr. Thiessen developed an electrode fabrication station that will produce electrodes for biocompatibility testing in Year 2		Contribution:	Mr. Crofts developed the wireless testing stations and built assemblies for verifying data and power transmission
Name:	Christopher Smith		Name:	Daniel McDonnall
Project Role:	Mechanical Engineer		Project Role:	PI – Research Scientist
Months:	2		Months:	2
Contribution:	Mr. Smith designed the ceramic package that was tested in Year 1		Contribution:	Dr. McDonnall directed research efforts in Year 1
Name:	Ginger Neil		Name:	Kenneth Guillory
Project Role:	Q&A/Regulatory		Project Role:	Systems Engineer
Months:	2		Months:	2
Contribution:	Ms. Neil coordinated testing per MIL standards of implant materials		Contribution:	Mr. Guillory helped design the wireless transmission system
Name:	Scott Hiatt			
Project Role:	Electrical Engineer			
Months:	2			
Contribution:	Mr. Hiatt developed the architecture for the wireless systems tested in Year 1			

Change in active other support

Scott Hiatt is partially supported by a new TATRC project; however, it will not interfere with this project.

Organizational partners

Nothing to report